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### [Intervention Review]

# Immunostimulants for preventing respiratory tract infection in children

Blanca Estela Del-Rio-Navarro<sup>1</sup>, Francisco J Espinosa-Rosales<sup>2</sup>, Vicki Flenady<sup>3</sup>, Juan JL Sienra-Monge<sup>1</sup>

<sup>1</sup>Department of Allergy and Immunology, Hospital Infantil de México "Federico Gómez", Mexico City, Mexico. <sup>2</sup>Department of Immunology, Instituto Nacional de Pediatría (National Institute of Pediatrics), México D.F., Mexico. <sup>3</sup>Translating Research Into Practice (TRIP) Centre - Mater Medical Research Institute, Mater Health Services, Woolloongabba, Australia

**Contact address:** Blanca Estela Del-Rio-Navarro, Department of Allergy and Immunology, Hospital Infantil de México "Federico Gómez", Dr. Marquez 162, Colonia de los Doctores, Mexico City, DF, CP 06720, Mexico. blancadelrionavarro@gmail.com, blancadelrionavarro@yahoo.com.mx.

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# ABSTRACT

#### Background

Acute respiratory tract infections (ARTIs) are a major cause of childhood morbidity and mortality. Immunostimulants (IS) may reduce the incidence of ARTIs.

# Objectives

To determine the efficacy and safety of IS in preventing ARTIs in children.

#### Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2011, issue 1, which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1966 to February week 4, 2011), EMBASE (1990 to February 2011), Google Scholar (2009 to February 2011), Scopus (2009 to February 2011), PASCAL (1990 to February 2010), SciSearch (1990 to February 2010) and IPA (1990 to February 2010).

#### **Selection criteria**

We included all comparative randomized controlled trials (RCTs) which enrolled participants less than 18 years of age. The intervention was IS medication, administered by any method, compared to placebo to prevent ARTIS.

#### Data collection and analysis

We analyzed the outcome on ARTIs both as the mean number of ARTIs by group and as a percent change in the rate of ARTIs. We undertook meta-analyses using a random-effects model and presented results as mean differences (MD) with 95% confidence intervals (CI). Two review authors independently assessed the search results and risk of bias, and extracted data. A funnel plot suggested there may be publication bias in the identified trials.

#### **Main results**

Thirty-five placebo-controlled trials (4060 participants) provided data in a form suitable for inclusion in the meta-analyses. When compared with placebo, the use of IS was shown to reduce ARTIs measured as the total numbers of ARTIs (MD -1.24; 95% CI -1.54 to -0.94) and the difference in ARTI rates (MD -38.84%; 95% CI -46.37% to -31.31%). Trial quality was generally poor and a high level of statistical heterogeneity was evident. The subgroup analysis of bacterial IS, D53 and OM-85 studies produced similar results, with lower heterogeneity. No difference in adverse events was evident between the placebo and IS groups.



#### Authors' conclusions

This review shows that IS reduce the incidence of ARTIS by 40% on average in susceptible children. Studies in healthy children are not available. Although the safety profile in the studies was good, some IS may be unsafe. ARTI-susceptible children may benefit from IS treatment. Further high-quality trials are needed and we encourage national health authorities to conduct large, multicentre, double-blind, placebo-controlled RCTs on the role of IS in preventing ARTIs in children.

# PLAIN LANGUAGE SUMMARY

#### Immunostimulants to prevent acute respiratory tract infections in children

Acute respiratory tract infections (ARTIs) are responsible for 19% of all deaths in children younger than five years of age, mainly in lowincome countries in Africa, Asia and Latin America. In high-income countries ARTIs are among the most frequent illnesses, leading to 20% of medical consultations, 30% of days lost from work and 75% of antibiotic prescriptions. In the USA the total cost of non-influenza-related viral ARTIs is around \$40 billion annually, while the corresponding cost for influenza is US \$87.1 billion. The main signs and symptoms of ARTIs include sneezing, runny nose, sore throat, cough and malaise. Children living in rural communities, not attending daycare centres, suffer about seven ARTI episodes in the first year of life; eight ARTIs per year from the ages of one to four; six per year aged five to nine; and five per year aged 10 to 19. Children exposed to risks factors, such as attendance at daycare centres, overcrowding, contact with older siblings, smoking at home and lack of breast feeding, may suffer more ARTIs.

Several treatments have been used to reduce the incidence of ARTIs (vitamin A, vitamin C, zinc, antibiotics). Among them are immunostimulants (herbal extracts, bacterial extracts, synthetic compounds), which aim to increase the immune defences of the respiratory tract. We searched for clinical trials of immunostimulants to prevent ARTIs in children compared to placebo. Our review includes 35 studies with 4060 participants. However, the quality of many of the studies was poor and the results were very diverse.

By combining results, immunostimulants reduced 1.24 ARTIs in a six-month period, equivalent to a 39% reduction in ARTIs compared to the placebo group. Only 20 studies provided adequate data on adverse events: the most frequent were rash, nausea, vomiting, abdominal pain and diarrhea. The main limitations of this review were the poor methodological quality and diverse trial results. We conclude that ARTI-susceptible children may benefit from immunostimulants, but more high-quality studies are needed. We suggest that national health authorities conduct high-quality randomized controlled trials to assess the true effects of immunostimulant preparations.